International Journal of Cardiology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Prognostic impact of residual stenosis after percutaneous coronary intervention in patients with ischemic heart failure – A report from the CHART-2 study☆

Kiyotaka Hao [a], Jun Takahashi [a], Yasuhiko Sakata [a], Satoshi Miyata [b], Takashi Shiroto [a], Kotaro Nochioka [a], Masanobu Miura [a], Takuya Oikawa [a], Ruri Abe [a], Masayuki Sato [a], Shintaro Kasahara [a], Hajime Aoyanagi [a], Hiroaki Shimokawa [a,b,*], on behalf of the CHART-2 Investigators

[a] Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan
[b] Department of Evidenced-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

ARTICLE INFO

Article history:
Received 23 February 2018
Received in revised form 9 September 2018
Accepted 17 October 2018
Available online xxxx

Keywords:
Residual coronary stenosis
Percutaneous coronary intervention
Heart failure
Left ventricular ejection fraction

ABSTRACT

Background: Complete revascularization with PCI is not always achieved in patients with ischemic HF. Therefore, this study aimed to elucidate the prognostic impact of residual coronary stenosis (RS) after percutaneous coronary intervention (PCI) in patients with ischemic heart failure (HF).
Methods: We analyzed a total of 1307 patients with symptomatic HF and a history of PCI registered in our Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) Study. RS that was defined as the presence of ≥70% luminal stenosis in major coronary arteries at the last coronary angiography.
Results: Among the study population, 851 patients (65.1%) had RS. During a median follow-up period of 3.2 years, patients with RS had higher all-cause mortality than those without it even after propensity score matching (21.9 vs. 11.6%, log-rank P = 0.027). Multivariable Cox hazard analysis also showed the negative impact of RS on all-cause death in ischemic HF patients [hazard ratio (HR):1.62, 95% confidence interval (CI): 1.07–2.46, P = 0.024]. Importantly, when divided all subjects into three subgroups by left ventricular ejection fraction (LVEF) [LVEF < 40% (HFrEF), LVEF 40–49% (HFmrEF), and LVEF ≥ 50% (HFpEF)], inverse probability of treatment weighted method provided a similar result that RS after PCI was an independent risk factor for death in the HFpEF [HR(95%CI); 1.94(1.22–3.09), P < 0.01] and HFmrEF [4.47(1.13–14.98), P < 0.01] groups, but not in the HFrEF group [1.20(0.59–2.43), P = 0.62].
Conclusions: These results indicate that RS after PCI could aggravate long-term prognosis of ischemic HF patients with moderate- to well-preserved EF, but not those with reduced EF.

1. Introduction

Heart failure (HF) is an epidemic healthcare problem worldwide, as called HF pandemic [1]. In particular, an increase in the incidence of HF has been reported in patients with acute myocardial infarction, in exchange of improved mortality due to better implementation of coronary reperfusion therapies and evidence-based medications [2]. Also in Japan, we demonstrated the temporal trend for increasing incidence of acute myocardial infarction but decreasing incidence of in-hospital mortality during the last three decades [3]. We also demonstrated an increase in the prevalence of coronary artery disease (CAD) as an etiology of HF in our Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2) Study [4]. Thus, CAD is the major cause of chronic HF worldwide [4,5].

For patients with moderate to large myocardial ischemia, the coronary revascularization strategy with percutaneous coronary intervention (PCI) and/or coronary artery bypass graft surgery (CABG) is indicated to ameliorate myocardial ischemia and cardiac function [6,7]. Although complete revascularization is ideally desirable in those patients, it is not always achieved in clinical practice, especially in patients with PCI as compared with those with CABG [8]. Moreover, incomplete revascularization after PCI has been associated with an increased risk of adverse cardiovascular events in several observational studies [9,10], and subgroup analyses of randomized trials [11]. However, in the subjects of those studies, patients with overt HF were the minority or excluded from the enrollment. Then, it remains to be fully elucidated whether residual coronary stenosis (RS) after PCI impacts on the long-term prognosis of patients with chronic and symptomatic ischemic HF. In the present study, we thus addressed

☆ All authors takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1, Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan.
E-mail address: shimo@cardio.med.tohoku.ac.jp (H. Shimokawa).

https://doi.org/10.1016/j.ijcard.2018.10.062
0167-5273/

this important issue in our CHART-2 Study, one of the largest prospective observational multicenter cohort studies in the world [4,12–14].

2. Methods

2.1. The CHART-2 study

The CHART-2 Study is a prospective observational multicenter cohort study, and details of the study design have been described previously (NCT00418041) [4,12–14]. Briefly, in the CHART-2 Study, 10,219 consecutive stable patients aged ≥ 20 years with either CAD (Stage A HF as defined according to the ACC/AHA guidelines [15], n = 868), asymptomatic structural heart disease (Stage B HF, n = 4514), or a current or past history of symptomatic HF (Stage C/D HF, n = 4837) were registered from the 24 participating hospitals between October 2006 and March 2010. The diagnosis of HF was made by attending experienced cardiologists based on the criteria of the Framingham study [16]. All of the patient information, including demographic, medical history, laboratory, echocardiographic and angiographic data, was recorded at the time of enrollment, and thereafter clinical information has been reviewed annually by trained clinical research coordinators. The study protocol was approved by the local ethics committee of each participating hospital and written informed consent was obtained from all patients (UMIN:000000562).

2.2. Study design

In the present study, we enrolled the patients with chronic and symptomatic ischemic HF who had received at least one prior treatment with PCI. The study flowchart is shown in Fig. S1. Among all cases of the CHART-2 Study, 4859 patients had a current or previous history of symptomatic HF. In those stage C/D HF patients, 2452 had ischemic heart disease defined by the presence of CAD or a history of previous myocardial infarction. From these patients, we excluded the patients as follows; those who did not receive any revascularization (n = 467), those who underwent CABG (n = 411), and those without any angiographic data (n = 267). Then, we finally evaluated 1307 patients with ischemic HF and a history of PCI. RS after PCI was defined as the presence of ≥70% diameter stenosis in major epicardial coronary arteries or >50% diameter left-main trunk stenosis observed at the last coronary angiography at the time of enrollment [17]. RS was visually evaluated by attending experienced cardiologists. Hypertension, dyslipidemia and diabetes mellitus were diagnosed based on the guidelines of the Japanese Society of Hypertension [18], Japan Atherosclerosis Society [19], and Japan Diabetes Society [20], respectively. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 [21]. Anemia was defined as hemoglobin < 12 g/dL in females and <13 g/dL in males [22]. In order to examine the prognostic impact of left ventricular ejection fraction (LVEF) in patients with RS after PCI, we divided them into three groups by LVEF, based on the 2016 ESC guidelines [23]; HF with reduced EF (HFrEF; LVEF < 40%, n = 169), HF with mid-range EF (HFmrEF;40 ≤ LVEF < 50%, n = 225), and HF with preserved EF (HFpEF; LVEF ≥ 50%, n = 818).

2.3. Statistical analysis

Continuous variables were expressed as mean ± SD or median with interquartile range as appropriate, and were compared by Welch's *t*-test. Categorical variables were expressed numeral with percentage, and were compared by the Fisher's exact test. Incidence of all-cause death was estimated using Kaplan–Meier curves and were compared by the log-rank tests. To reduce confounding effects related to differences in baseline characteristics between patients with and without RS in this observational study, propensity score (PS) methods were used in combination with Cox regression model. For the calculation of PS, we used a logistic regression model in which the presence of RS was regressed for the following 21 baseline characteristics; age, sex, body mass index, systolic blood pressure, heart rate, hypertension, diabetes mellitus, dyslipidemia, current smoking, previous myocardial infarction (MI), previous stoke, atrial fibrillation, CKD, anemia, LVEF, serum levels of B-type natriuretic peptide (BNP), use of beta-blockers, angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), statins, antiplatelets. Goodness-of-fit of the logistic model was confirmed by the area under the curve (AUC) of receiver operating characteristic (ROC) curve, and the Hosmer-Lemeshow decile test. Kaplan-Meier curves were also plotted to evaluate the association between RS and all-cause death in the PS-matched cohort using the PS-stratified Cox analysis. Furthermore, to reduce confounding in the time-to-event observational data, multivariable inverse probability of treatment weighted (IPTW) Cox modeling was also used [12,24]. To examine the determinants of all-cause death, we used multivariable Cox proportional hazard model and calculated Hazard ratio (HR) and 95% confidence intervals (CI). We selected 22 potential confounding factors (21 baseline characteristics described above and the presence of RS) by using stepwise variable selection procedure. When performing subgroup analysis, the interaction between RS and predefined clinical subgroups in their effects on all-cause death was assessed by the Cox model with interaction terms.

A P-value of <0.05 and a P-value for interaction of <0.10 were considered to be statistically significant. All statistical analysis was performed using IBM SPSS Statistics 18.0 (IBM, Somers, NY, USA) and R software (version 3.0.3) (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient characteristics

Among 1307 patients with stable and overt ischemic HF, 851 (65.1%) had RS after PCI. Baseline characteristics of the study population are presented in Table 1. Patients with RS were characterized by lower proportion of female, higher prevalence of prior stroke and anemia, higher level of BNP, and more frequent use of beta-blockers. On the other hand, several factors, such as systolic blood pressure, heart rate, prevalence of prior MI and atrial fibrillation, and LVEF, were comparable between the groups with and without RS. After performing PS matching for the entire population, 332 matched pairs of patients were identified. For the logistic model to estimate PS, AUC of ROC curve was equal to 0.650 and the Hosmer-Lemeshow test provided P = 0.372. After PS matching, baseline characteristics became generally comparable between the 2 groups (Table S1).

3.2. Clinical outcomes and prognostic impact of residual coronary stenosis

Kaplan-Meier curves for all-cause mortality of the unmatched and PS-matched populations during a median follow up period of 3.2 years are shown in Fig. 1. In the entire population, all-cause mortality was significantly higher in the patients with RS as compared with those without it (22.2 vs. 11.6%, P < 0.001) (Fig. 1A). Interestingly, the patients with multi-vessel RS tended to have a poor prognosis as compared with those with single-vessel RS (28.0 vs. 16.8%, P = 0.071) (Fig. S2A), whereas the presence of chronic total occlusion (CTO), left descending artery (LAD) lesion, or proximal lesion had no significant prognostic impact (Fig. S2B, C, D). After performing the PS matching, a higher incidence of all-cause death was still noted in the patients with RS (21.9 vs. 11.6%, P = 0.027) (Fig. 1B). Moreover, as shown in Table S2, the stepwise multivariable Cox regression analysis also selected the presence of RS as a predictor for all-cause death in patients with ischemic HF [HR (95%CI); 1.62(1.07–2.46), P = 0.024], in addition to other 7 prognostic factors, including age, anemia, diabetes mellitus, heart rate, BNP, systolic blood pressure, and statin use. To elucidate whether RS generated a harmful effect in any specific conditions, univariable Cox model for all-cause death was applied to clinical subgroups identified by patient characteristics. As shown in Fig. S3, the Cox model consistently showed that a worse outcome caused by RS was generally applicable in any subgroups, including age, sex, diabetes mellitus, previous MI, atrial fibrillation, CKD, anemia, and serum levels of BNP. Accordingly, RS did not significantly interact with any of those factors.

3.3. Prognostic impact of residual coronary stenosis by LVEF

We then examined the prognostic impact of RS by LVEF in the patients with echocardiography data available at the time of enrollment (n = 1212). The prevalence of HFrEF, HFmrEF, and HFpEF was 13.9% (n = 169), 18.6% (n = 225), and 67.5% (n = 818), respectively. Among the three groups, the percentage of patients with RS was comparable (HFrEF, 67.5%; HFmrEF, 61.8%; and HFpEF, 64.9%; P = 0.492). Baseline characteristics of the entire population by LVEF are summarized in Table S3. HFmrEF patients essentially had intermediate characteristics between HFpEF and HFrEF patients. In fact, from HFrEF, HFmrEF, to HFpEF, age, body mass index, NYHA class, systolic blood pressure, and prevalence of hypertension were increased significantly, whereas heart rate, prevalence of atrial fibrillation and CKD, serum level of BNP, prescription rates of beta-blockers and ACEI were decreased. The cumulative incidence of all-cause death by the presence or absence of RS for each ischemic HF type is shown in Fig. 2. Intriguingly, although the patients with RS had a worse prognosis than those without it in the HFpEF and HFmrEF groups (HFmrEF, 24.4 vs. 9.9%, P = 0.008; HFpEF, 20.3 vs. 10.6%, P = 0.005), we found no prognostic difference between patients with and without RS in the HFrEF group (29.8 vs.

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Table 1
Baseline characteristics of the study population.

	(−) RS (n = 456)	(+) RS (n = 851)	P value
Age (years)	68.7 ± 11.3	69.9 ± 10.5	0.07
Female sex, n (%)	110 (24.1)	156 (18.3)	0.01
Body mass index (kg/m^2)	24.1 ± 3.4	24.1 ± 3.4	0.98
SBP (mm Hg)	127.4 ± 17.9	128.7 ± 18.8	0.25
Heart rate (/min)	70.2 ± 13.1	70.9 ± 13.2	0.40
NYHA class, n (%)			0.21
I	159 (35.0)	252 (29.3)	
II	260 (57.3)	525 (62.2)	
III	32 (7.0)	67 (8.2)	
IV	3 (0.7)	3 (0.3)	
Medical history, n (%)			
Hypertension	412 (90.4)	794 (93.3)	0.07
Diabetes mellitus	206 (45.2)	418 (49.1)	0.18
Dyslipidemia	411 (90.1)	786 (92.4)	0.18
Current smoking	77 (18.0)	181 (22.4)	0.08
Previous MI	369 (80.9)	651 (76.5)	0.08
Previous stroke	66 (14.5)	183 (21.5)	0.002
Atrial fibrillation	84 (18.4)	180 (21.2)	0.25
Chronic kidney disease	198 (43.8)	423 (50.1)	0.04
Anemia	130 (28.7)	340 (40.2)	<0.001
Laboratory data			
LVEF (%)	56.6 ± 14.1	56.1 ± 14.2	0.62
BNP (pg/mL)	59.6 (25.6–147.3)	93.4 (34.8–231.2)	0.001
Medications, n (%)			
Beta-blockers	213 (46.7)	450 (52.9%)	0.04
ACEI	183 (40.1)	384 (45.1)	0.09
ARB	143 (31.4)	296 (34.8)	0.22
Statins	288 (63.2)	538 (63.2)	1.00
Antiplatelets	427 (93.6)	811 (95.3)	0.24
Residual coronary stenosis, n (%)			
Number of vessels			
0 vessel	456 (100%)		
1 vessel		492 (57.8)	
2 vessels		259 (30.4)	
3 vessels or left main trunk		100(11.8)	
Locations			
Left descending artery		522 (61.3)	
Left circumflex artery		366 (43.0)	
Right coronary artery		395 (46.4)	
Left main trunk		17 (2.0)	
Chronic total occlusion		211 (24.8)	
Time from CAG to enrollment (day)	533 (111–1353)	180 (19–886)	<0.001

Continuous variables are expressed as mean ± standard deviation, except BNP levels, which are expressed as median with interquartile range.
Chronic kidney disease was defined as an estimated glomerular filtration rate < 60 mL/min/1.73 m^2. Anemia was defined as hemoglobin < 13 g/dL in males and <12 g/dL in females.
ACEI = angiotensin converting enzyme inhibitors; ARB = angiotensin II receptor blockers; BNP = B-type natriuretic peptide; CAG = coronary angiography; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; RS = residual coronary stenosis; SBP = systolic blood pressure.

29.5%, P = 0.619). The IPTW method based on the weights given by the multinomial PS also provided a similar result that RS after PCI was associated with the incidence of all-cause death in HFpEF and HFmrEF patients, but not in HFrEF patients [adjusted HR(95%CI): HFrEF, 1.04 (0.62–1.75), P = 0.885; HFmrEF, 3.90 (1.57–9.69), P = 0.003; HFpEF, 1.47 (1.07–2.03), P = 0.019] (Table 2).

4. Discussion

In the present study, we examined the prognostic impact of RS after PCI in patients with stable and symptomatic ischemic HF in our CHART-2 Study, which is the largest prospective observational study for chronic HF in Japan. The present study showed that; (1) RS after PCI was significantly associated with the incidence of all-cause death in patients with overt ischemic HF, (2) the prognostic impact of RS after PCI was equally noted even if the subjects were divided into various subgroups by age, sex, diabetes mellitus, previous MI, atrial fibrillation, and CKD, with the exception for LVEF, and (3) patients with RS after PCI had a higher mortality in ischemic HFpEF and HFmrEF groups, but not in ischemic HFrEF group, who had a worse prognosis irrespective of the presence of RS.

4.1. Prognostic impact of residual stenosis in patients with coronary artery disease

PCI is a frequently used revascularization procedure for CAD patients. However, incomplete revascularization occurs more frequently in PCI patients than in patients treated with CABG [8]. Even in the era of drug-eluting stents, incomplete revascularization was performed in 69% of multivessel CAD procedures enrolled in the New York State registry study [9]. Thus, although several studies addressed the prognostic importance of PCI in HF patients, the results were inconsistent. Previous randomized control trials showed that in patients with STEMI and multi-vessel disease, multi-vessel PCI significantly reduced a risk of adverse coronary event as compared with revascularization of culprit lesion alone [25–27]. For patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS), a small observational study did not show any difference in the incidence of adverse cardiac event between patients with and those without RS [28], whereas the post-hoc analysis of the ACUITY trial showed that RS was associated with an increased risk of adverse coronary events [11]. In patients with stable CAD, RS also has been shown to be associated with an increased risk of long-term mortality after PCI [9,10]. However, in those studies, the majority of study population had no overt HF. Thus, in the present study, we examined the prognostic impact of significant RS in patients with overt ischemic HF and a history of PCI in our CHART-2 Study, where we noted the presence of RS in two-thirds of our entire subjects. In general, the reasons for incomplete PCI may include the presence of one or more chronic total occlusions, the presence of serious medical conditions such as severe CKD or severe LV dysfunction, or the decision to treat only the "culprit lesion" that is thought to be responsible for the symptoms. In fact, in the present study, as compared with ischemic HF patients without RS, those with RS were more likely to have a history of stroke, renal insufficiency, anemia, and high serum levels of BNP, and to be treated with beta-blockers. These results suggest that the patients with RS have more serious atherosclerotic change and HF. To account for those differences in baseline characteristics between the patients with and those without RS after PCI, we have used multivariable and PS analyses. Accordingly, even after adjustment for baseline differences, patients with RS had a worse prognosis than those without it. Furthermore, RS after PCI independently correlated with an incidence of death in patients with overt ischemic HF, in addition to other established predictors of HF, such as age, anemia, diabetes mellitus, heart rate, serum levels of BNP, systolic blood pressure, and statin use [13]. Thus, our findings that RS after PCI could be an important prognostic factor for future risks could be useful in the management of patients with ischemic HF. In the present study, due to the large-scale nature of the study with many participating hospitals, severity of residual stenosis (RS) was evaluated through visual confirmation but by experienced cardiologists. Thus, we were unable to assess the severity and complexity of RS quantitatively with residual SYNTAX score or SYNTAX revascularization index, which are useful for predicting the mortality [29]. Furthermore, functional assessment with fractional flow reserve (FFR) is more important to predict adverse cardiovascular events than angiographical assessment. A recent study also supported the importance of functional complete revascularization with FFR guidance [30]. Thus, a prospective randomized trial with FFR measurement for RS after PCI is needed to further evaluate the clinical importance of complete revascularization in patients with ischemic HF.

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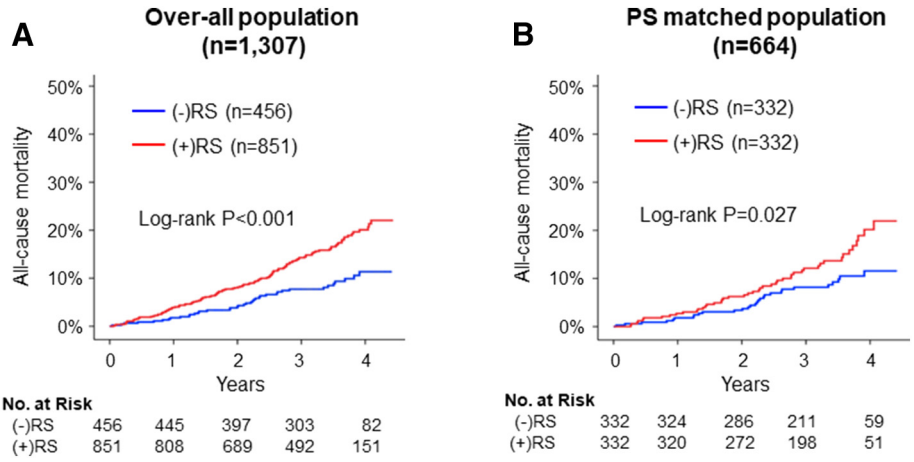

Fig. 1. Kaplan-Meier curve for cumulative all-cause mortality in patients with ischemic HF. All-cause mortality of patients with and those without residual stenosis in overall population (A) and PS matched population (B). PS, propensity score.

4.2. Relationship between residual coronary stenosis and LVEF in ischemic HF patients

The 2016 ESC guidelines proposed a new classification of chronic HF by LVEF; HFrEF (LVEF < 40%), HFmrEF (LVEF, 40–49%), and HFpEF (LVEF ≥ 50%) [23]. We thus examined the prognostic impact of RS after PCI by LVEF. The present results showed that RS was associated with poor prognosis in patients with HFmrEF and HFpEF, but not in those with HFrEF. This difference may be related to the amount of residual myocardium. In addition to the degree and complexity of anatomical burden of coronary atherosclerotic lesions, the myocardial viability is also an important factor for beneficial effect of revascularization. A previous study showed that myocardial viability evaluated by non-invasive testing was strongly associated with improvement of survival mediated by revascularization in patients with chronic CAD, whereas absence of myocardial viability resulted in no significant change in outcomes irrespective of treatment strategies [7]. Thus, viability of the myocardium perfused by the coronary artery with RS might influence the results of the present study; positive effects in ischemic HFmrEF and HFpEF, but not in HFrEF. In the present study, since we have no data about myocardial viability, we were unable to directly examine the effects of residual myocardial ischemia.

In addition to ischemic burden, the prevalence of HFpEF has been increasing recently [4,31]. In fact, nearly 70% of the present population was classified as HFpEF. However, effective strategies still remain to be established for the disorder [32]. The present finding suggests RS could be an additional therapeutic target for patients with ischemic HF. Indeed, it was previously reported that in 255 HFpEF patients with CAD, complete revascularization by PCI or CABG was associated with lower mortality compared with those with incomplete revascularization [33]. Furthermore, in the present study, the negative prognostic impact of RS after PCI was also noted in HFmrEF patients. We recently reported that clinical features of HFmrEF are intermediate between HFpEF and HFrEF, and a part of HFmrEF could dynamically transit to HFrEF mostly within 1 year [14]. Thus, we should consider to perform an additional revascularization therapy in patients with ischemic HFmrEF with RS before the transition to HFrEF, as there might be less prognostic impact of RS in this advanced stage.

4.3. Study limitation

Several limitations should be mentioned for the present study. First, in the present study, we defined RS as the significant stenosis at the last angiography at the time of enrollment. Thus, the follow-up period between the last angiography and the enrollment varied in each subject. Actually, it was significantly shorter in patients with RS as compared with those without RS, which might affect the results of the present study. However, it is important to note that patients with significant RS with shorther follow-up time had worse prognosis than those without it with longer follow-up time, suggesting that the difference in the

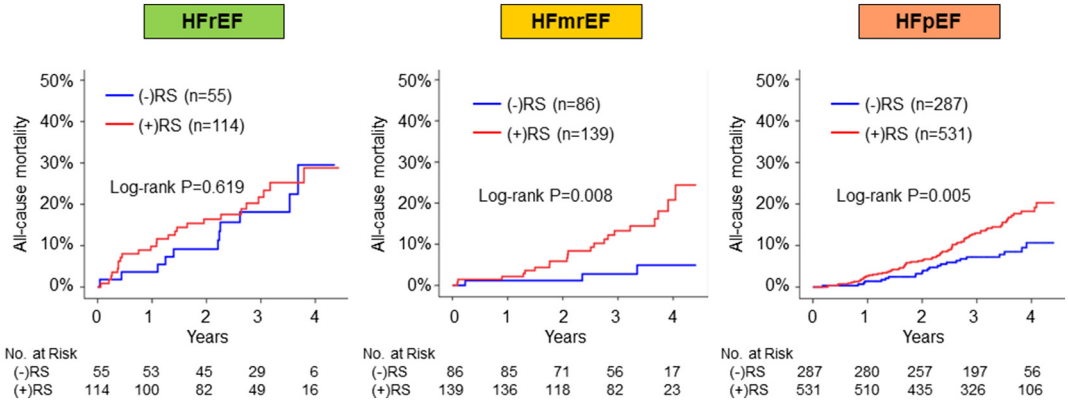

Fig. 2. Kaplan-Meier curve for cumulative all-cause mortality in patients with ischemic HF by LVEF. All-cause mortality was comparable between HFrEF patients with and those without residual stenosis. In contrast, it was significantly higher in HFmrEF and HFpEF patients with residual stenosis as compared with those without it. HF; heart failure, HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; RS, residual stenosis.

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Table 2
Unadjusted and adjusted hazard ratio of residual stenosis for all-cause death in patients with ischemic heart failure.

	Unadjusted		Adjusted	
	HR (95%CI)	P value	HR (95%CI)	P value
Overall population	1.95 (1.37–2.80)	<0.001	1.52 (1.18–1.97)	0.001
Patients with HFrEF	1.35 (0.59–3.06)	0.476	1.04 (0.62–1.75)	0.885
Patients with HFmrEF	4.63 (1.07–20.14)	0.041	3.90 (1.57–9.69)	0.003
Patients with HFpEF	1.95 (1.17–3.26)	0.011	1.47 (1.07–2.03)	0.019

Adjustment was performed by inversed probability of treatment weighted (IPTW) method with propensity score, using the following factors; age, anemia, atrial fibrillation, body mass index, BNP levels, chronic kidney disease, current smoking, diabetes mellitus, dyslipidemia, heart rate, hypertension, LVEF, previous MI, previous stroke, residual coronary stenosis, SBP, sex, use of beta-blocker, ACEI, ARB, statins, and antiplatelets.
ACEI = angiotensin converting enzyme inhibitors; ARB = angiotensin II receptor blockers; BNP = B-type natriuretic peptide; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; SBP = systolic blood pressure.

follow-up time between the 2 groups had minor prognostic impact. Second, in the CHART-2 Study which is a cohort study for patients with HF, we had no data about angina status (e.g. CCS class) or prior PCI procedures (e.g. stenting or ballooning). Moreover, in the CHART-2 study, since treatment decision for revascularization strategy were left to attending experienced cardiologists in each institution, we were unable to determine why complete revascularization was not attempted in individual patient with RS. Third, in the present study, no data were available concerning myocardial viability or myocardial ischemic burden. It was previously reported that myocardial viability and ischemic burden are strongly associated with improvement of survival by revascularization in CAD patients [6,7]. Moreover, guidelines for PCI recommend us to assess myocardial viability to decide the therapeutic strategy in CAD patients [34]. The presence or absence of myocardial viability or myocardial ischemic burden in the territory perfused by the coronary artery with RS could affect the results of the present study. Actually, our finding that the prognostic impact of RS was documented in patients with ischemic HFmrEF and HFpEF, but not in those with HFrEF, suggests the importance of myocardial viability. Fourth, the present study was conducted as an observational design, and the management decisions were left to the discretion of each attending physician. Although we performed propensity score-matched analysis to adjust for potential confounders between the patients with and those without RS, the observational nature of this study might limit its validity. Fifth, although anatomical definition for RS was used in several previous studies [9,10], due to the large-scale nature of the present study with many hospitals, no data were available regarding length of the lesion, morphology, dominancy of the vessels, presence of collaterals, or atherosclerotic burden patterns. Thus, we were unable to assess the degree and complexity of RS quantitatively with residual SYNTAX score or SYNTAX revascularization index, which are useful for predicting the mortality [29]. Moreover, no functional assessment such as FFR was not carried out in the present study. Sixth, it the present study, we did not examine the impacts of antithrombotic therapies essential for the management of ischemic heart disease. In particular, as discussed in the COMPASS and COMMANDER HF trials [35,36], the effectiveness of direct oral anti-coagulants in ischemic HF patients remains to be controversial. The present findings could help to classify the candidates who could benefit from the new antithrombotic therapy among ischemic HF patients with prior PCI.

5. Conclusions

In patients with ischemic HF, the prognostic impact of RS after PCI varies according to LVEF. RS after PCI is associated with poor prognosis in patients with HFmrEF and HFpEF, indicating that HFmrEF and HFpEF patients with RS could benefit from further revascularization.

Grants and financial support

This study was supported in part by Grants-in Aid from the Ministry of Health, Labour and Welfare, the Ministry of Education, Culture, Sports, Science and Technology (H.S. and Y.S.), and the Agency for Medical Research and Development (H.S.). The Department of Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, is supported in part by unrestricted research grants from Daiichi Sankyo Co., Ltd. (Tokyo, Japan), Bayer Yakuhin, Ltd. (Osaka, Japan), Kyowa Hakko Kirin Co., Ltd. (Tokyo, Japan), Kowa Pharmaceutical Co., Ltd. (Tokyo, Japan), Novartis Pharma K.K. (Tokyo, Japan), Dainippon Sumitomo Pharma, Co., Ltd. (Osaka, Japan), and Nippon Boehringer Ingelheim Co., Ltd. (Tokyo, Japan). H.S. has received lecture fees from Bayer Yakuhin, Ltd., (Osaka, Japan), Daiichi Sankyo Co., Ltd. (Tokyo, Japan) and Novartis Pharma K.K. (Tokyo, Japan).

Acknowledgements

We thank all the members of the Tohoku Heart Failure Society and the staff of the Departments of Cardiovascular Medicine and Evidence-Based Cardiovascular Medicine for their collaboration (Supplementary Appendix S1).

Funding

This study was supported in part by Grants-in Aid from the Ministry of Health, Labour, and Welfare, the Ministry of Education, Culture, Sports, Science, and Technology (H.S. and Y.S.), and the Agency for Medical Research and Development (H.S.).

Conflict of interest disclosures

The Department of Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, is supported in part by unrestricted research grants from Daiichi Sankyo Co., Ltd. (Tokyo, Japan), Bayer Yakuhin, Ltd. (Osaka, Japan), Kyowa Hakko Kirin Co., Ltd. (Tokyo, Japan), Kowa Pharmaceutical Co., Ltd. (Tokyo, Japan), Novartis Pharma K.K. (Tokyo, Japan), Dainippon Sumitomo Pharma, Co., Ltd. (Osaka, Japan), and Nippon Boehringer Ingelheim Co., Ltd. (Tokyo, Japan). H.S. has received lecture fees from Bayer Yakuhin, Ltd., (Osaka, Japan), Daiichi Sankyo Co., Ltd. (Tokyo, Japan) and Novartis Pharma K.K. (Tokyo, Japan).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.10.062.

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Please cite this article as: K. Hao, et al., Prognostic impact of residual stenosis after percutaneous coronary intervention in patients with ischemic heart failure – A report..., Int J Cardiol (2018), https://doi.org/10.1016/j.ijcard.2018.10.062